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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

SEPTEMBER 1938

EXPERIMENTAL HYPERTENSION INDUCED BY RENAL ISCHEMIA

Harvey Lecture, May 19, 1938

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ALTHOUGH the direct method for the determination of blood pressure in animals dates back to Stephen Hales,[1] in 1733, and although the existence of a state of increased vascular tension in man was surmised on the basis of indirect methods, especially palpation of the pulse,[2] pulse tracings[3-5] and other bloodless indirect methods,[6-8] yet it was not until the development by Riva-Rocci[9] of the method of taking blood pressure (actually bursting tension) by the pneumatic cuff and mercury manometer that the existence and significance of human hypertension were fully recognized and the serious study of its cause was undertaken.

Whether or not disease of the kidneys plays a primary part in the pathogenesis of increased arterial tension has been the subject of speculation and controversy for a long time. More than 100 years ago, before blood pressure had been determined in man, Richard Bright[10,11] observed the frequent coexistence of renal disease of various kinds and hypertrophy

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of the heart for which he found no obvious cause in the heart or large blood vessels. He attributed the cardiac hypertrophy to an effect produced on the heart (increased action) or blood vessels (increased peripheral resistance) by an altered state of the blood which, he felt convinced, was caused by the renal disease, although he admitted the possibility that the renal disease might be the result of the altered state of the blood. Thus, although Bright knew nothing about hypertension, we now realize that he was the first to consider the possible renal origin of this condition. He tried to perfuse nodular kidneys and mentioned the resistance which the nodules offered to injection. Toynbee[12] found that this difficulty was due to thickening of wall and narrowing of lumen of the smaller intrarenal arteries. This has since been fully confirmed by direct[13-16] and indirect[17-19] methods. Johnson[20] showed that in such cases similar thickening in the small arteries was present in other organs; yet he offered the theory that the primary disease was within the kidney, and that cardiac hypertrophy and increased arterial tension were due to generalized constriction of the peripheral branches of the arterial system. For the vasoconstriction he had a far-fetched teleological explanation to the effect that the vascular disease would interfere with the passage of accumulated noxious substances from the blood into the tissues. Traube[2] was the first to express the definite view of a primary causative relationship between renal disease and increased arterial tension. This was based on the mechanical theory of the resistance which the disease in the kidneys offers to the loss of water from the blood and also to the amount of blood leaving the aorta, with consequent hydremia and increased arterial tension. This view has not been substantiated by subsequent authors except those who have used his theory as a basis for a teleological explanation of hypertension. It was principally as a result of the anatomical studies of Gull and Sutton,[21] who demonstrated the rather widespread distribution of organic disease of the smallest branches of arteries and the capillaries, which they called arteriocapillary fibrosis, that these generalized organic changes were seriously considered as the primary cause of increased peripheral resistance, with consequent hypertension and cardiac hypertrophy. The clear differentiation of chronic glomerulonephritis and renal arteriolar sclerosis[22,23] finally led to the recognition of Frank's[24] essential hypertension. The hypertension associated with chronic glomerulonephritis was quite generally regarded as renal in origin so that the problem became limited to the pathogenesis

of essential hypertension. To the followers[25,26] of Gull and Sutton, the cause of the hypertension appeared to have been explained, but there remained the problem of the cause of the primary vascular disease. The pendulum swung when it was realized that the organic disease of the arterioles, even in the most severe cases, was not sufficiently widespread to account for the increased peripheral resistance that is required to cause persistent hypertension. Huchard[27] and Allbutt[28] projected the idea that the hypertension, due to generalized vasoconstriction, is the primary manifestation and the organic vascular disease a consequence of this condition. Mueller[29] went so far as to assert that prolonged vasoconstriction in a localized zone, such as the splanchnic, could be the cause of essential hypertension. The problem then became one of finding the cause of such generalized or localized vasoconstriction, with the kidney not seriously considered as the primary source of this effect. Both groups considered the vascular disease of the kidney simply a part of the generalized disease process and did not assign to it a primary part in the origin of this type of hypertension.

It is now generally accepted that hypertension may be of renal origin but this is usually assigned to the hypertension that accompanies obstructive disease of the urinary passages, chronic glomerulonephritis, polycystic kidney, renal panarteritis and severe renal amyloidosis.[30] Yet there are those, like Kylin,[31,32] who go so far as to deny the renal origin of hypertension under all conditions and who regard the various types of renal disease accompanying hypertension as secondary or merely coincidental. Fishberg[30] has defined essential hypertension as persistently elevated blood pressure without known cause which, on neither clinical nor anatomical grounds, can be considered due to inflammatory or obstructive renal disease. Although Fishberg includes various types of hypertension in this category, yet by far the commonest is the type associated with so-called diffuse vascular disease. Most of the recent writers[36-40] on the subject have assigned this term to this condition and agree with Fishberg that it is not of renal origin. The usual arguments against the renal origin of essential hypertension have been: (a) the frequent discovery of elevated blood pressure before there are any recognizable signs of impairment of renal function;[42] (b) the fact that in a large percentage of these cases renal insufficiency never does become manifest; and (c) the failure to find any anatomical signs of renal disease in some of these cases. Fishberg,[33] Bell and Clawson,[34] and Moritz

and Oldt[35] have found that at autopsy there is organic arteriolar disease in the kidneys of most individuals who have had essential hypertension, without signs of renal functional damage during life. Yet only Moritz and Oldt,[35] the most recent investigators of this phase, have drawn the conclusion from their results that the vascular disease of the kidney must be seriously considered as playing a primary part in the pathogenesis of essential hypertension. In the reports of cases of essential hypertension in which no intrarenal arteriolar disease was found,[30] the possibility was not usually excluded that severe sclerosis in some portion of the main renal arteries might have been the cause of renal ischemia. During the past year, in a few cases of hypertension without renal arteriosclerosis, severe sclerosis and narrowing of the orifice or lumen of the main renal arteries or the lumen of the larger extrarenal branches, obviously sufficient to cause renal ischemia, have been observed.[41] Formerly lesions of this kind have probably been overlooked and the cases classified as essential hypertension without renal vascular disease.

Experimental evidence or proof for the view that the kidney may play a primary part in the development of hypertension has been sought in a variety of ways that appear in the following summary:

A SUMMARY OF OTHER EXPERIMENTS DESIGNED TO DETERMINE THE POSSIBLE RENAL ORIGIN OF HYPERTENSION

Bilateral nephrectomy.

Mosler[43] (1912). Used rabbits. Insignificant elevation of blood pressure.
Backmann[44] (1916). Used cats. No elevation of blood pressure.
Cash[45] (1926). Used dogs. No elevation of blood pressure.
Hartwich[46,47] (1930). Used dogs. No elevation of blood pressure.
Harrison, Blalock and Mason[139] (1929, 1936). Used dogs. No elevation of blood pressure in 16 out of 18 dogs.

Reduction of the amount of functioning renal tissue.

Grawitz and Israel[49] (1879). Used rabbits. Slight hypertrophy of heart, interpreted by the authors as due to hypertension.
Pässler and Heineke[50] (1905). Used dogs. Slight elevation of blood pressure.
Backmann[44] (1916). Used cats. Slight elevation of blood pressure.
Allen and collaborators[51] (1925). Used dogs. Slight temporary elevation of blood pressure.
Mark[52a,b] (1925, 1928). Used dogs. Slight elevation of blood pressure.
Anderson[54] (1926). Used rabbits. No elevation of blood pressure.
Hartwich[46,47] (1929, 1930). Used dogs. No elevation of blood pressure.
Friedmann and Wachsmuth[55] (1930). Used dogs. No elevation of blood pressure.
Chanutin and Ferris[56] (1932). Used rats. Great elevation of blood pressure.
Wood and Ethridge[86] (1933). Used rats. Hypertension.
Rytand and Dock[57] (1935). Used rats. Great elevation of blood pressure.

Reduction of amount of renal substance by coagulation necrosis due to ligation of branches of renal arteries.

Janeway[58,59] (1908, 1913), assisted by Carrel[53] (1909). Used dogs. Slight elevation of blood pressure.

Mark[52b] (1928). Used dogs. No elevation of blood pressure.

Hartwich[46,47] (1929, 1930). Moderate elevation of blood pressure. Not persistent.

Friedmann and Wachsmuth[55] (1930). Moderate elevation of blood pressure. Not persistent.

Reduction of amount of renal substance by partial renal excision and unilateral nephrectomy combined with coagulation necrosis of part of the remaining kidney by ligation of branches of renal artery.

Cash[60] (1924). Used dogs. Slight to moderate temporary elevation of blood pressure.

Hantschmann[69] (1931). Used dogs. Slight elevation. Not persistent.

Mark and Giesendörfer[61] (1930). Used dogs. Moderate temporary elevation of blood pressure.

Ferris and Hynes[62] (1931). Used dogs. Slight temporary elevation of blood pressure.

Destruction of renal substance by irradiation of kidneys with roentgen rays.

Hartman, Bolliger and Doub[63] (1926). Used dogs. Moderate elevation of blood pressure.

Page[89] (1935). Used dogs. Moderate elevation of blood pressure.

Renal infarction due to multiple emboli.

Senator[65] (1911). Used cats. Injected liquid paraffin into renal arteries. No rise of blood pressure.

Cash[60] (1924). Used dogs. Injected insoluble Berlin blue. No elevation of blood pressure.

Apfelbach and Jensen[66] (1931). Used dogs. Injected particles of charcoal into renal arteries. No elevation of blood pressure.

Occlusion of one main renal artery.

Hartwich[46,47] (1929, 1930). Used dogs. Slight temporary elevation of blood pressure.

Friedmann and Wachsmuth[55] (1930). Used dogs. Slight temporary elevation of blood pressure.

Occlusion of both main renal arteries.

Katzenstein[67] (1905). Used rabbits and dogs. No rise of blood pressure.

Cash[45] (1926). Used dogs. Moderate to severe elevation of blood pressure.

Occlusion (permanent or intermittent) of renal arteries, veins and ureters.

Cash[45] (1926). Permanent occlusion. Used dogs. No elevation of blood pressure.

Loesch[68] (1933). Intermittent brief occlusion, every two or three days. Used dogs. Moderate persistent elevation of blood pressure.

Partial constriction of renal arteries (acute experiments).

Katzenstein[67] (1905). Used dogs. Very slight elevation of blood pressure.

Bridgman, E. W. and Hirose, K.[74] (1918). Used dogs. No elevation of blood pressure.

Passive hyperemia (constriction of renal vein) of one kidney.

Pedersen[64] (1927) and Bell and Pedersen[70] (1930). Used dogs. Moderate temporary elevation of blood pressure.

Menendez[71] (1933). Used dogs. Slight temporary elevation of blood pressure in some; none in others.

Compression of kidneys by oncometer.

Alwens[72] (1909). Used cats. Acute experiments. Slight elevation of blood pressure.

Permanent obstruction of ureters.

Hartwich[46,47] (1929, 1930). Used dogs. Moderate elevation of blood pressure.

Harrison, Mason, Resnik and Rainey[73] (1936). Used dogs. Moderate elevation of blood pressure.

Temporary obstruction of one ureter followed by release of obstruction and excision of other kidney.

Rautenberg[75] (1910). Used rabbits. Moderate elevation of blood pressure.

Effect of nephrotoxic substances.

Dominguez[76] (1928). Used rabbits. Injected uranium salts. No elevation of blood pressure except in one animal that developed severe arterial and arteriolar sclerosis, especially in the kidneys.

Arnott and Kellar[77,78] (1935, 1936). Used rabbits. Injected sodium oxalate. Moderate temporary elevation of blood pressure.

Scarff and McGeorge[79] (1937). Used rabbits. Injected sodium oxalate. No elevation of blood pressure.

In some of the earlier investigations mentioned in the summary the hypertension that was observed was usually slight and lasted from only a few hours to several days. Some of the later investigators reported the development of hypertension of moderate degree and of short duration while others succeeded in producing moderate or severe hypertension of longer duration. Under practically every heading contradictory reports occur. Some of these experiments merely proved what is generally accepted, even for man, namely, the renal origin of hypertension associated with obstruction of the urinary passages or great destruction of renal parenchyma.[30] The contradictory results obtained by different investigators were due partly to the various methods, some indirect, like cardiac hypertrophy, which were used for determining the existence of hypertension, the different types of animal employed and the slight changes of blood pressure which were regarded as significant by some and not by others. For some of the contradictory results[77,78,79] there is no obvious explanation. The results of the experiments performed up to

1928 did indicate that various pathological changes in the kidneys could in some way play a primary part in initiating a degree of at least temporary hypertension in animals. By none of these methods was the condition produced in the kidneys comparable to that of the kidneys in human essential hypertension associated with arteriolar disease. It would appear that those experiments that were designed to prove the renal origin of essential hypertension failed for several reasons: 1. They were acute experiments and yielded negative or contradictory results in the hands of different investigators using the same methods. 2. In most of the chronic experiments, the experimental conditions did not reproduce or even simulate the anatomical or functional state of the kidneys in benign essential hypertension. 3. Hypertension, when produced, did not persist. Any method for the experimental determination of the possible primary part played by renal arteriosclerosis in the origin of essential hypertension should involve the production of at least the physiological effect of the renal vascular disease. It is not actually known, but it is at least probable, that the effect is a decrease of the flow of blood to the functioning elements of the kidney and a decrease in the intraglomerular capillary pressure. The latter would not be correct if the view is valid that there is spasm of the efferent arterioles[80] or the capillaries[81] of the glomeruli in essential hypertension.

Up to 1928, when the experimental investigations of the author were begun, no one had succeeded in producing either generalized arteriolar sclerosis or arteriolar sclerosis limited to the kidneys. For these investigations, therefore, the following working hypothesis was adopted: If organic disease of the kidney be the initiating factor in the pathogenesis of benign essential hypertension, then this disease is, in all probability, the arteriolar sclerosis which is so frequently associated with this condition. If arteriolar sclerosis limited to the kidneys can be the primary factor in initiating this type of hypertension, then the necessary conditions for the establishment of the renal origin of essential hypertension upon an experimental basis should be the production of hypertension in animals by any method which will produce at least the physiological effects of such renal vascular disease. Since there is no known way of producing arteriolar sclerosis localized to the kidney, it was thought that the effects of arteriolar disease could probably be produced by constricting the main renal arteries. Katzenstein,[67] and Bridgman and Hirose[74] did try to produce hypertension by constricting the main renal arteries, but the experi-

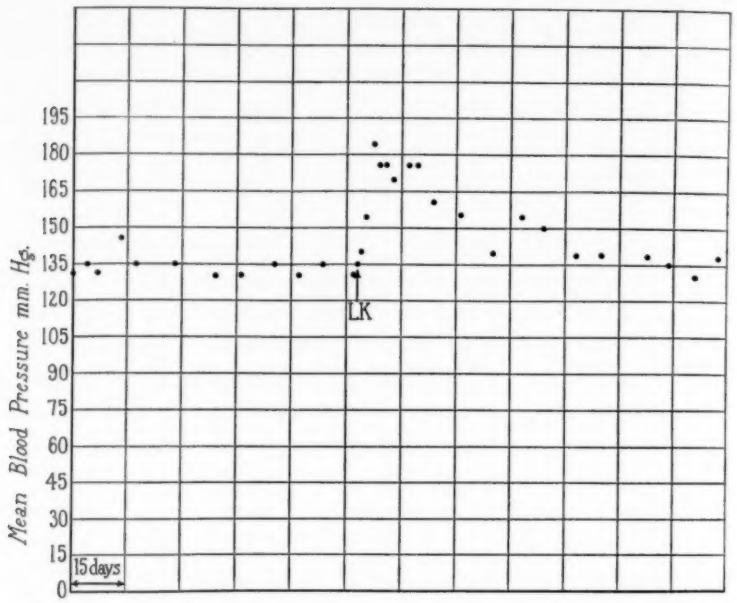

Fig. 1—Dog-3-35, male, chow, young. Initial weight 12.4 kg. Final weight 14.0 kg. LK = left main renal artery—moderately constricted. ● = Mean blood pressure, mm. Hg, direct method, femoral artery.

ments were very short and their results contradictory. Bridgman and Hirose observed no elevation and Katzenstein a very slight rise (10 mm. Hg.) of mean blood pressure. For the purpose of the author's experiments, a special type of silver clamp was devised[83] whereby the main renal arteries could be constricted and their lumina reduced to any desired caliber. It was first demonstrated[83] that decrease of the lumen of the main renal artery by varying degrees of compression caused an immediate corresponding decrease of blood flow through the kidney. Whether the decreased blood flow persists after hypertension develops has not yet been determined. A decrease of intraglomerular capillary pressure as a result of this procedure has been assumed but not proved.

In a series of experiments, by the use of this method, it has been found that, in the dog[82,83,84] and monkey,[85] constriction of the main artery of one kidney results in elevation of blood pressure which persists from weeks to months but usually returns to a lower or to the original level within one month (Fig. 1). The adequate constriction of both

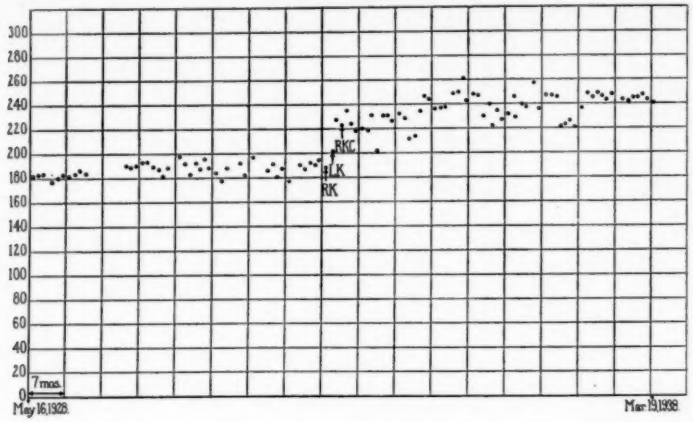

Fig. 2—"Blackie", short-haired mongrel, female, age about 1 year, in 1928. Initial weight 21.4 kg. Present weight 21.6 kg. RK = moderate constriction of right main renal artery. LK = moderate constriction of left main renal artery. RKC = occlusion of right main renal artery. The animal is still alive. ● = Systolic blood pressure, mm. Hg, van Leersum carotid loop method.

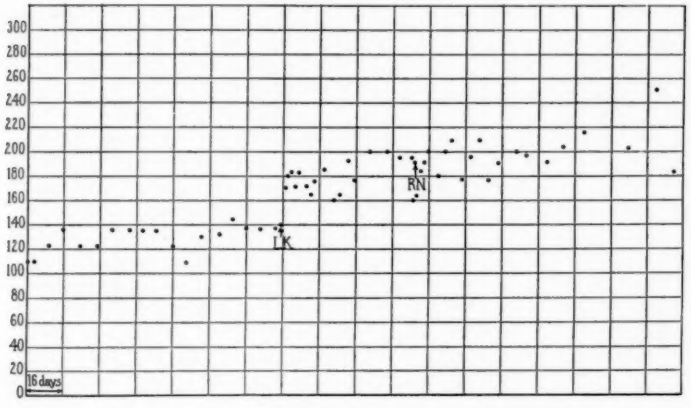

Fig. 3—Dog 3-14, male, bull-dog, young. Initial weight 11 kg. Present weight 11.8 kg. LK = severe constriction of left main renal artery. RN = right nephrectomy. ● = Mean blood pressure, mm. Hg, direct method, femoral artery.

main renal arteries at the same time, or with an interval between the clampings, results in persistent hypertension (Fig. 2). The same persistent effect on blood pressure has been obtained by first constricting the main artery of one kidney and later removing the other kidney (Fig. 3). In

some animals with both renal arteries constricted, the elevated blood pressure also tends after a while to return to a lower level. This is probably due to the development of significant accessory circulation to the kidney, which is naturally abundant in the dog.[210] In such dogs, increasing the constriction of the main renal arteries usually results in re-elevation of blood pressure. In some dogs, collateral circulation has become so well established that one or both main renal arteries have been finally entirely occluded and such animals have survived several years with greatly elevated blood pressure without accompanying significant impairment of renal function. It has been shown that the hypertension which has been produced by these methods in dogs and monkeys involves elevation of both diastolic and systolic pressure.[84,85,91] A similar effect in the upper part of the body can be obtained by constricting the aorta immediately above the origin of both main renal arteries.[87] Indirect confirmation of this is the development of left ventricular hypertrophy in the rat after constriction of the aorta immediately above the origin of the renal arteries.[225] Contriction of femoral or splenic arteries,[46,47,48,83] of splanchnic arteries,[213] or the aorta immediately below the origin of both renal arteries[87] does not elevate blood pressure. Most of these results have now been fully confirmed and amplified by many investigators.[89-92,97,214]

When the constriction of both main renal arteries, the main artery of the only kidney, or the aorta above the origin of the renal arteries is made moderate, there is no accompanying disturbance of renal function, detectable by the usual studies of urine and blood, including urea and creatinine clearance tests.[83,84,85] In some of the animals, with the main renal arteries constricted, the hypertension has persisted at a very high level for more than five years (Fig. 2). In the animals with the aorta constricted above the origin of both main renal arteries there has been a much greater tendency to return to the original level. In these, in order to make the hypertension persist, it has been found necessary also to constrict the aorta below the renal arteries. Despite this additional procedure, the accessory circulation to the kidney appears to be adequate to interfere with persistence of the hypertension at a high level.[87] In those animals that have had long standing hypertension, without accompanying damage of renal function, the only significant changes in the vascular system observed so far have been degenerative changes, mainly intimal, in the arterioles of the retina[93] and thickening of the media of the arterioles

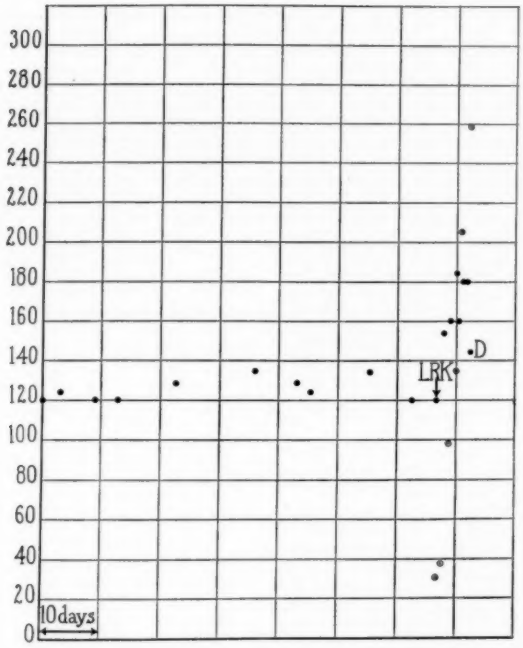

Fig. 4—Dog 3-90, female, mixture of collie and airdale, middle-aged. Initial weight 10.9 kg., final weight 12.2 kg. LRK = almost complete constriction of left and right main renal arteries. D = died. ● = Mean blood pressure, mm. Hg, direct method, femoral artery. ⊙ = Blood urea nitrogen, mg. per 100 cc. of plasma.

in other organs, especially skeletal muscle. The changes in the kidneys affect mainly the tubules. The organ may show but little change[99] or may undergo atrophy, depending upon the severity of the constriction.[83,84] In such animals hypertrophy of the heart has been reported.[92,99]

If the constriction of the renal arteries or of the aorta is made severe or complete from the beginning, disturbance of renal function usually accompanies the elevated blood pressure and the animal may develop fatal uremia.[83,84,85] In some of these animals (Fig. 4) there develop widespread fibrinoid and hyaline degeneration, and necrosis of arterioles, with petechiae in some organs, similar in all respects to the lesions observed in the acute malignant phase of essential hypertension in man (see Plate).

The mechanism of development of the benign phase of experimental

hypertension induced by renal ischemia has now been the subject of extensive investigation. In considering the pathogenesis of this type of hypertension it has been assumed, for the same reasons as for human essential hypertension,[30,94] that the responsible mechanism is increased peripheral resistance. Since, in the experimental animals, this cannot be regarded as due to initial organic change in the peripheral portion of the entire vascular system, the problem narrows down to the cause of the functional increase of peripheral resistance which follows the constriction of the main renal arteries. The teleological explanation[208] of purposeful increase of peripheral resistance in order to elevate the pressure and improve the blood flow through the ischemic kidneys is not susceptible to proof. There are, therefore, but two known mechanisms whereby the generalized constriction of arterioles[30] and increased peripheral resistance can be produced; namely, either a nervous reflex from the ischemic kidneys, which affects the general vasomotor apparatus, or a humoral mechanism initiated by the ischemic kidneys due to the formation or accumulation in the blood of a substance which, directly or indirectly, constricts the peripheral vessels. The possibility that such a substance might act on capillaries[96] or by neutralizing a natural depressor substance must also be mentioned.

That the ischemic kidneys are in some way directly responsible for the development of the experimental hypertension has been shown by

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*EXPLANATION OF PLATE**

This Colored Plate Represents a Photomicrograph in color Prepared by the Separation Method.

Fig. 1—Arteriole in submucosa of large intestine. Beginning subendothelial deposit of hyalin. Endothelium well preserved. Hematoxylin and eosin. ×265.

Fig. 2—Arteriole in submucosa of stomach. Obliterative hyalinization of intima, endothelium still recognizable but nuclei reduced in number and pyknotic. Hematoxylin and eosin. ×430.

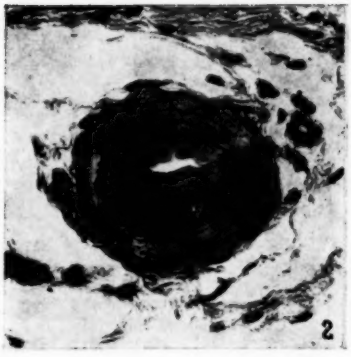
Fig. 3—Arteriole in submucosa of small intestine. Lumen completely obliterated by accumulation of hyalin containing a few pyknotic nuclei. Hematoxylin and eosin. ×430.

Fig. 4—Arteriole in submucosa of stomach. Portion of entire thickness of wall necrotic. Normal thickness of wall and lumen natural size. Hematoxylin and eosin. ×325.

Fig. 5—Arteriole, cut longitudinally, in submucosa and mucosa of large intestine. Partly hyalinized, partly necrotic, with extravasated blood around it. A portion of the same arteriole, in the submucosa, immediately proximal to the part included in this figure, was entirely normal. Hematoxylin and eosin. ×255.

* This colored plate reprinted from the *Journal of Experimental Medicine*. Vol. 67, No. 5, 1938.

1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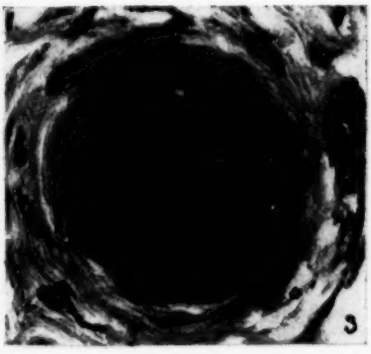
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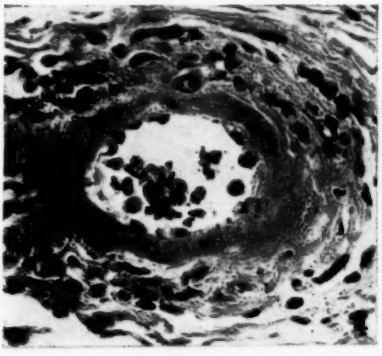

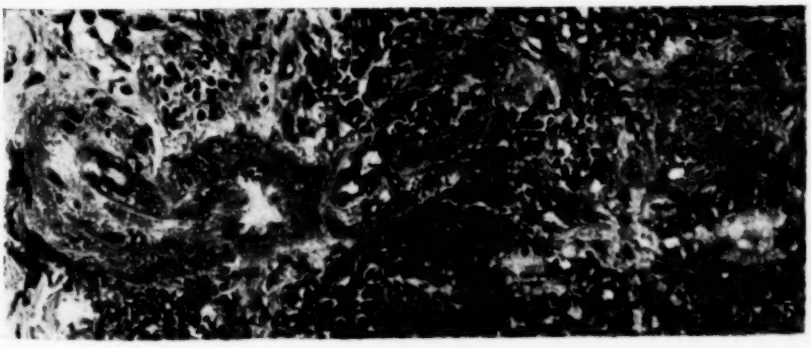

the following experiments. If the main renal artery of one kidney is constricted and the ischemic kidney is removed some time later, when the blood pressure is still well elevated, the blood pressure falls promptly to the normal level.[84] If, instead of nephrectomy, the clamp on the one ischemic kidney is released or removed, the blood pressure also returns promptly to the original level.[84] If the elevated blood pressure is first produced by the constriction of the main renal arteries of both kidneys, and only one clamp is released, the blood pressure falls slowly to the lower or to the original level in about the same time that it does when only one clamp is applied.[84] If, in a hypertensive animal, both clamps are released, the blood pressure falls promptly to the original normal level.[84] If one kidney is transplanted to the neck or inguinal region and the other kidney removed, constriction of the arterial blood supply to the transplanted kidney results in the development of elevated blood pressure.[97,98] Bilateral nephrectomy is not followed by the development of persistent hypertension.[43-48,84] These results constitute evidence that the kidney is responsible for the effect and that it must be present in the body in order for the hypertension to occur.

The experiments that have been directed toward the study of the possible part played by a nervous reflex from the kidney have failed to establish this as the mechanism responsible for the increased peripheral resistance. In dogs, denervation of the renal pedicle[89,92,99] does not prevent or reduce hypertension due to constriction of the main renal arteries. This differentiates this type of hypertension from that due to intracisternal injection of kaolin[105] which can be prevented or reduced to normal by renal denervation. In the case of hypertension due to denervation of the carotid sinus and section of the depressor nerves the results of investigations of the effect of renal denervation have been contradictory.[108] Section of splanchnic nerves and excision of the lower four thoracic sympathetic ganglia,[100] section of the anterior nerve roots from the sixth dorsal to the second lumbar inclusive,[101] excision of the entire sympathetic nervous system in thorax and abdomen, including cardiac denervation,[102-104] and even pithing,[98] have failed to prevent, or permanently to reduce hypertension produced by constriction of the main renal arteries. Finally, as mentioned above, if one kidney is removed and the other kidney is transplanted to the neck or to the inguinal region, and its main renal artery is constricted, elevated blood pressure develops.[97,98] In such an animal there is no possible direct connection between

kidney and nervous system. The results of these studies eliminate a nervous reflex from the ischemic kidneys as the responsible mechanism for the initiation of the hypertension and leave only a humoral mechanism as the probable explanation of the phenomenon. These experiments do not eliminate the possibility that in human essential hypertension stimuli from the central nervous system may sometimes play a primary part and often an accessory part in elevating blood pressure above the level determined by the renal mechanism. It is probably the nervous factor which is influenced by the usual medical treatment of hypertension and accounts for any fall of blood pressure which results.

The failure of the various surgical procedures carried out on the nervous system to affect experimental hypertension due to constriction of the main renal arteries is probably due to the persistence of the effect on the kidney which cannot be materially altered by these procedures as long as the clamp remains applied. These experiments do not in any way controvert the results that have been obtained by the same procedures in the surgical treatment of hypertension in man.[112-125,188] They do emphasize, however, the importance of the renal factor as the primary cause of this type of experimental hypertension and probably of human essential hypertension that is associated with renal arteriolar disease. Since the renal factor in man is frequently due to narrowing of the lumen of only the arterioles of the kidney, without narrowing of the lumen of the large arteries, improvement of the circulation might result from the various surgical operations on the nervous system, as a result of relaxation of those arterioles in which the organic changes are not fixed. The lowering of blood pressure reported in about the same percentage of cases of hypertension by surgeons using various procedures which, directly or indirectly, affect the vasomotor nervous mechanism in the abdomen may, therefore, be due mainly to one cause; namely, the improvement of the circulation through the kidneys, and not, as has been suggested, directly to the relaxation of the arterioles in a large part of the vascular bed of the abdomen, independently of any effect on the kidneys. The latter view has no support in experimental observations.

All of the investigations that have been directed toward the study of the pathogenesis of this type of experimental hypertension have yielded results that indicate the existence of a humoral mechanism of renal origin that is responsible for the vascular constriction and consequent increased peripheral resistance which produces the elevation of the blood pressure.

Removal of both kidneys does not result in elevated blood pressure, although the animal develops severe azotemia.[43-48,84] On the contrary, sudden occlusion of the main renal artery of both kidneys, which also results in fatal uremia, does produce hypertension.[45,84] Since occlusion of both main renal arteries does not eliminate all circulation to the dog's kidneys,[210] a chemical substance might still be washed from the kidney into the general circulation. That this is most probably the case is shown by the failure of hypertension to develop when both main renal veins are occluded at the same time that the main renal arteries are constricted or occluded.[84] This is due, presumably, to interference with the entrance of the hypothetical chemical substance into the blood stream. If the ischemic kidney from one animal is transplanted to the neck of a nephrectomized animal, the blood pressure of the latter rises almost immediately after the circulation through the ischemic kidney is restored, while the transplantation of a normal kidney has no effect on the blood pressure.[126,127] This has been interpreted as an indication that some chemical present in considerable concentration in the ischemic kidney, suddenly washed into the circulation of the recipient animal, produces an almost immediate pressor effect. Whether such a "hypothetical effective substance"[84] actually exists and what its nature is has not yet been elucidated. The normal kidney does not acquire this pressor substance in the short period during which it is without circulation before the transplantation is completed.[126,127]

Since the original investigation by Tigerstedt and Bergmann,[128] who obtained a pressor effect with saline extract of normal rabbits' kidneys, when they injected it intravenously into other rabbits, many workers have repeated the experiments with different kinds of extracts, expressed juices and autolysates of normal kidneys of various animals, with conflicting results. Some[129,130] confirmed Tigerstedt and Bergmann's finding; others[131-133] obtained only depressor effects; while most investigators[134-138] found both a depressor and pressor effect, the latter usually following the former. Pressor effects have also been obtained with extracts from other organs.[142] The search for the possible chemical substance involved in the humoral mechanism of renal origin in the cause of experimental hypertension due to constriction of renal arteries has resulted in a number of investigations that have dealt with the presence of a pressor principle in normal and ischemic kidneys. Tigerstedt and Bergmann actually suggested[128] that there might be an increase

of the pressor substance, *rennin* they called it, in the kidneys of hypertensives. The recent isolation by Landis and collaborators[224] of an extract of normal kidney which elevates blood pressure without diminishing skin temperature and without reducing the amplitude of arterial pulsation is of special interest. A similar extract of ischemic kidney should be made and compared quantitatively with the extract of normal kidney.

Several investigators[139,140,211] have reported a larger amount of pressor substance in the watery extract of ischemic kidneys of experimental hypertension due to constriction of main renal arteries and of the arteriosclerotic kidneys of human hypertension as compared with that of normal kidneys. This does not constitute proof that this is the pressor principle involved in the production of hypertension which follows constriction of the main renal arteries or in essential hypertension in man.

Attempts to demonstrate a direct pressor substance in the systemic or renal venous blood or extract of the plasma of animals with experimental hypertension due to constriction of the main renal arteries have failed.[143] This differs from the result obtained with blood from animals with experimental hypertension due to the intracisternal injection of kaolin.[209] The results of tests made on the blood in human essential hypertension, both benign and malignant, have been contradictory; some obtained pressor effects[144-172] and others did not;[173-184] and the transfusion of blood in large quantity from a hypertensive individual to one with normal blood pressure had no effect on the blood pressure of the latter.[185] The pitfalls of investigations of this kind have been emphasized by O'Connor.[186] Thus there is no conclusive proof of the existence of a known or new pressor substance in the blood, spinal fluid, or urine in human essential hypertension, although it has been possible to obtain a pressor effect with blood from cases of paroxysmal hypertension associated with pheochromocytoma.[226]

The possible part played by the endocrine organs in the humoral mechanism of experimental hypertension due to renal ischemia has been the subject of investigation. Page and Sweet[187] have obtained contradictory results on the influence of hypophysectomy on this type of hypertension. Whereas the removal of the hypophysis had little or no influence in preventing this type of hypertension, yet hypophysectomy in hypertensive dogs was followed by a fall of blood pressure to a lower or normal level in some of the animals. The latter result may have been due to the development of adequate accessory circulation to the kidney

and may not have been due to the effect of hypophysectomy. This investigation requires repetition.

The influence of the adrenals has also been studied.[84] The possibility of keeping bilaterally adrenalectomized dogs alive by means of substitution and supportive therapy[189-193] has permitted the performance of a series of experiments on the effect of constricting the main renal arteries of such animals. Briefly, the results have shown that bilateral adrenalectomy without supportive or substitution therapy prevents the development of hypertension due to renal ischemia and causes previously produced hypertension to fall promptly to the normal or to a subnormal level. The result is the same even when supportive treatment in the form of sodium chloride and sodium bicarbonate or sodium citrate is given to the adrenalectomized animals. However, when presumptive substitution therapy in the form of cortical extract, as well as supportive treatment, is given, some of the animals do develop elevated blood pressure despite the absence of both adrenals. That it is the cortex and not the medulla of the adrenals that is important in this connection is shown by experiments in which one adrenal was completely removed, the medulla of the remaining adrenal destroyed, and the entire cortex[83] or only a small portion of it[84] left just sufficient to maintain life. In such animals, the blood pressure became elevated in the usual way when the main renal arteries were constricted. The results of many of the above experiments have already been confirmed[97] and Rogoff and collaborators[227] have shown recently that there is no increase of epinephrine secretion in this type of experimental hypertension. Just how the cortical hormone acts is not elucidated by these experiments. It may act only by playing its usual part in the physiological mechanisms and by insuring a normal state of the blood vessels of the animal. It may produce its effect by sensitizing the blood vessels to the action of the hypothetical effective substance of renal origin, or the reverse. The two substances may act synergistically. These are points that remain to be clarified. What these experiments do indicate is the futility of surgical[194-200,227] or other procedures designed to cure or lower hypertension in man by removal of one or destruction of portions of both adrenals, except in cases of paroxysmal hypertension associated with tumor of the adrenals.[201-207,226]

Nothing is known about the pathogenesis of the arteriolar degeneration and necrosis which are found in many internal organs, but most

frequently in the kidneys[30] and gastrointestinal tract,[35] in human benign or malignant hypertension. The degenerative and necrotizing arteriolar lesions of the animals which have been described above are not distinguishable from those found in most cases of malignant hypertension in man[35] except that they are more severe and more widespread than in the latter. This indicates a greater susceptibility of the dog's arterioles to these changes. In human malignant hypertension, skeletal muscles and lungs also rarely show necrosis of arterioles, although hyalinization and other changes may occur in those of the muscles.[216] The only striking difference between the lesions in man and dog is that in the latter the kidneys do not, while in the former they very frequently do show arteriolar necrosis. This discrepancy is easily explained and actually affords a clue to the pathogenesis of this lesion. In the animals, the intravascular pressure, within the kidney, is low, because the ischemia is due to the constriction of the main renal artery. In man, the intrarenal vascular tension is undoubtedly high, because there is sclerosis and constriction of the preglomerular arterioles. In some of the larger vessels of the human kidney the lumen is also frequently narrowed, due to proliferation of the intima, but it has never been shown that the arterioles belonging to such vessels become necrotic. It may be that only those arterioles become necrotic that are subjected to the high bursting tension as well as to the hypothetical toxic substance or substances in the blood which result from the renal insufficiency. There are some human cases in which necrosis of small renal arterioles is not found. These may be cases in which the renal insufficiency is due to widespread intimal proliferation in the small arteries and large arterioles and not to the reduction in the caliber of the preglomerular arterioles. This may also account for the difference and point to one of the probable factors and necessary conditions in the pathogenesis of arteriolar necrosis and hemorrhage; namely, elevated pressure within these vessels. That the accumulation of chemicals in the blood is not by itself a sufficient condition for the production of the arteriolar lesions, is shown by the fact that bilaterally nephrectomized dogs that develop azotemia but no hypertension[84] do not develop the generalized hyalinization and necrosis of arterioles and associated hemorrhages in the organs. That hypertension alone is not sufficient to determine the formation of the necrotizing lesions of the arterioles is shown by the fact that animals that have had severe hypertension for more than five years, without accompanying significant

disturbance of renal excretory function, have not developed this lesion. That the lesions of the arterioles are not due to ischemia is shown by the absence of the lesions from the severely ischemic kidneys of the dogs and their presence in organs in which there is no preexistent ischemia. In the dogs, at least, the combination of hypertension and severe disturbance of renal function, with consequent accumulation of chemical substances in the blood, is at least a necessary condition for the manifestation of the arteriolar necrosis and associated hemorrhages in various organs. Since the hypertension is not present within the intrarenal blood vessels of the animals with the main renal arteries, or the aorta above the origin of the renal arteries, constricted, the lesion does not manifest itself there. The same explanation (absence of local hypertension) probably applies to the absence of the lesion in the pulmonary arterioles of man as well as of animals. What the nature of the chemical substance or substances is that plays a part in the production of these lesions is not elucidated by these investigations on experimental hypertension that have been carried out so far but they do show that hypertension, severe disturbance of renal excretory function, and generalized degenerative changes, including severe hyalinization and necrosis, of the arterioles, all indistinguishable from those found in the malignant phase of hypertension in man, can be induced experimentally by severe reduction of the blood supply to the kidneys.

The results of all the investigations that have dealt with the pathogenesis of the benign phase of experimental hypertension due to constriction of the main renal arteries apply equally well to the malignant phase. The only experimental condition that determines the type of hypertension is the degree of constriction of the main renal arteries.

One obvious surgical therapeutic procedure which suggests itself as the result of this work is the possible improvement of blood supply to the functioning components of the kidney by increasing the accessory circulation. In the animals with experimental hypertension induced by renal ischemia, whenever there is a return of the blood pressure to a lower level, it is due to inadequate initial clamping of the renal arteries or to the development of effective accessory circulation by way of ureteral and capsular vessels, which become very prominent. If, before constricting the renal artery, the kidney is decapsulated and adipose tissue or muscle is attached to the denuded cortical surface, the accessory circulation becomes very prominent and interferes with the development of

pronounced elevation of blood pressure. Since in the animals the constriction is only of the main renal artery, such accessory circulation can be of functional significance. The fact that animals have survived several years the complete closure of both main renal arteries,[84] when effected gradually by increasing the constriction at intervals, is proof that such accessory circulation can be functionally highly effective. Unfortunately, in human essential hypertension, the vascular disease most frequently involves also the preglomerular arterioles, so that collateral communication with the larger vessels would not improve circulation to glomeruli. Whether improvement of blood supply to some glomeruli, to tubules and interstitial tissue would occur and whether it would be effective in lowering blood pressure in human essential hypertension cannot be determined without trying. Although the author has hesitated to recommend it, yet there is probably more justification on an experimental basis for making this test than there has been for some of the surgical procedures that have already been practiced. The cases in which the production of accessory circulation would be most effective would be those in which the hypertension is due to sclerosis of the main renal arteries alone[41] or their very large branches. The difficulty of making such a diagnosis is obvious, so that unless the method could be applied to essential hypertension associated with renal arteriolar sclerosis the procedure would be of greatly restricted value.

An interesting practical application of this work, which centers upon the renal origin of so-called essential hypertension, has been the finding in children[217] and adults[218] of hypertension associated with unilateral pyelonephritis and vascular disease, and the prompt return of the blood pressure to normal after excision of the diseased kidney.[217,218] Until 1930, according to Bell and Pedersen[219] hypertension associated even with bilateral pyelonephritis had not been reported. Since then several authors[220-223] have reported this occurrence in some cases and from the meager studies of the kidneys in these cases it becomes probable that the hypertension associated with unilateral or bilateral pyelonephritis in children and adults occurs only in those cases in which there is associated vascular sclerosis or in which the inflammatory disease produces the same effects on renal circulation as does vascular disease. In cases of unilateral arteriolar nephrosclerosis with hypertension, which have been reported by Moritz and Oldt,[35] if the diagnosis could be made in life, removal of the diseased kidney might result in a return of the

blood pressure to normal, as in the cases of unilateral pyelonephritis.* Unfortunately, unless the production of accessory circulation would be effective, nothing but transplantation of a normal kidney or kidneys, with removal of both diseased kidneys, could be expected to relieve the hypertension and prove the renal origin of the disease in cases of human hypertension associated with bilateral pyelonephritis or arteriolar sclerosis of the kidneys. Whether this can ever be accomplished in man, as it can in animals, is for the future to disclose.

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* From the James Buchanan Brady Urological Institute and Department of Medicine of Johns Hopkins Hospital there have just been reported[228,229] two cases of hypertension associated with unilateral renal vascular disease in which the removal of the diseased kidney resulted in a prompt return of the blood pressure to normal. A similar result has been obtained in a third unreported case (Personal Communication, Professor Hugh Young).

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ENDOSCOPIC PROSTATIC RESECTION*

JOSEPH FRANCIS MCCARTHY

THE title, Transurethral Resection, which seems to enjoy considerable usage, lacks precision and euphony and is a reversion to the era in medicine of resounding and ambiguous phraseology. "Endoscopic Prostatic Resection" has none of these defects. The term implies the removal through the urethra, with an endoscope, by means of an electrically charged cutting loop, or a punch, or both, of serial sections of obstructing prostatic tissue, the objective being the restoration of the normal canular character of the prostatic urethra in exaggerated degree. This was the concept of the writer at the inception of this work and it remains unchanged. A number of highly qualified urologists, however, entertain the conviction that what amounts to subtotal prostatectomy is or should be the desired objective.

The mortality in endoscopic resection is, generally speaking, lower than in open prostatectomy. If trustworthy statistics are submitted indicating that the late symptomatic results are as good as those of open prostatectomy, we shall be quite willing to revise this opinion.

In this operation, one must of necessity give heed not only to the gland itself but to the contiguous structures as well. The physiology, pathology and bacteriology are, or should be, matters of concern.

There is, it appears, a too casual acceptance and a disproportionate stressing of the obstructing phase of prostatism. The patient knows he has an increasing hindrance to the normal act of emptying his bladder, that because of the frequency of this act, his night's rest is disturbed, that he has or has not pain, or disability. He wants relief or cure by the simplest, the safest, and the least time-consuming method. Above all, he does not want an open surgical operation. This is especially pertinent to doctors so afflicted. Here is the first prostatic problem of today and the urologist has now not only the question of selection of method of procedure, but in the event this decision is not in accord with the patient's

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desire for instrumental methods, a still more difficult problem.

The whole subject of prostatism with its multi-faceted aspects, is a topic of ever increasing interest. Physical debility generally antedates mental senility, and because of the age range of these patients, we are dealing with a group who know their world and frequently are leaders in it. If, as is probably the case, 25 per cent of all men experience this trouble—individuals at the peak of their mental capacity though perhaps well on the road of physical decline—the minimal contribution to this tremendously important problem, on the part of those who regard themselves leaders of thought in this field, is complete detachment from preconceptions, personal predilections, prejudices, and aptitude for a given method.

My own experience with instrumental correction of established prostatism has been barometric, to say the least; moments of exaltation wherein the problem appeared to be completely solved. Errors of interpretation, of judgment or of technique occurred, however, with sufficient frequency to bring about the salutary conviction of the desirability of moderation. In a communication of several years ago, quoting from memory, I stated that endoscopic prostatic resection will not be fostered by unbridled enthusiasm, nor hindered by prejudiced neglect; that if it had intrinsic merit it would carry on of its own momentum. If it did not have such merit, time would reveal this defect. Now, some eight years later, the situation is somewhat as indicated in a recent communication in the *Journal of Urology:* "It has been interesting to note the varying trends of the time. In an increasing number of the larger clinics, a degree of enthusiasm is manifested for closed surgery, which at least equals that of the original proponents of these methods. The conclusion to be drawn from this situation is, that while technical ability and judgment are vital, a fine organization is of equal importance. Such at least is the deduction of the writer. Individuals, it should be pointed out, or the occasional adventurer in this field of endeavor, cannot hope to achieve such results. The other extreme of viewpoint is represented by a group of urologists of unquestioned ability, who relegate this type of surgery to a relatively minor rôle. Paradoxical as this appears, both are right. This last mentioned group have developed a high degree of skill in open surgery; results in their hands are better than with other methods. Such individuals must elect to serve a more or less prolonged apprenticeship, a period fraught with travail, with a coincidental higher mortality, developing facility

with technical methods to which they may not be adaptable, either temperamentally or by past experience. One elects to do that which one does best, whether it be tight rope walking or steeple climbing. Prostatics will, perhaps, be all the better for the pursuit of this practice." As an elaboration of this question, it may be stated that there is a much larger group who employ the method in a considerable percentage of prostatics, who regard it as a preferential procedure in selected cases. While it is an invaluable addition to the urologist's equipment, it is still supplemental and does not replace the various and longer established open methods.

There are two prime objectives in endoscopic resection; first, the removal of sufficient encroaching prostatic tissue to effect complete restoration of function, and to minimize the likelihood of recurrence. Second, the avoidance of injury to adjacent parts. These structures are the verumontanum externally, the trigon internally, the seminal vesicle through its ejaculatory ducts, and the external sphincter. Any operator in this field should be mindful of the following fundamentals. First, as previously reported, that while on the floor of the internal sphincter, there is a very considerable margin of safety; immediately posterior to this point, the safety factor is greatly reduced. Indiscriminate digging at this point with an electrically charged loop, may easily result in subtrigonal infection. It was for this reason that, in this part of the operation, we now employ the visualized punch instrument previously described in this journal. Injury to the veru may also be avoided by carefully adjusting the telescope so that the terminal of the sheath on the floor is within the visual field. This holds good for both punch and electrotome. Thus, one may observe precisely, the anterior limit of the cutting trajectory.

Considering the prostatic urethra as a circle, any experienced prostatectomist knows that the weakest part of that circle is its superior aspect. The technique of intra-urethral enucleation is based on this fact. One, therefore, should exercise the greatest caution in the removal of prostatic tissue, above ten and two on the clock. One personal experience of extravesical seepage as the result of too liberal tissue removal at this point, is the occasion for the suggestion. Moreover, one should have a precise appreciation of size and type of gland structure, by rectal palpation, immediately after the administration of the anesthetic and before the operation."

Preoperative Management

Preoperative study of these cases is particularly exacting. We are dealing with elderly men. The cardiovascular system, therefore, must be minutely investigated. Electrocardiograms should be routine. Diabetics and hypertensives, if one is to follow the dictates of prudence, should have a preparatory period during which every effort should be made to bring such individuals to their peak of resistance to any operative experience. Hypertensives especially should, whenever possible, be guarded against violent blood pressure fluctuations, inasmuch as the added foot pound pressure at blood vessel terminals may, and not infrequently does, present difficulties in the adequate arrest of bleeding without undue coagulation.

Preoperative Infections

I have never been able to subscribe to the commonly held belief that these patients are all the better for the presence of an infected urine, with its inevitable corollary, an infected prostate. If such theory ever had any merit in open prostatectomy, which I seriously doubt, how can it be supported where the operation is performed in a closed and highly permeable canal wall such as lines the prostatic urethra? I use No. 10 or 12F. catheter decompression with a Drummond irrigator; and regulation of the hydrogen-ion content of the urine, which any intelligent nurse can report with the newer kinds of quantitative litmus and chlorophenol red, with colorimetric charts. With modern medication, the hydrogen-ion content of the urine can thus be regulated with almost test tube accuracy. This is a much more scientific form of management than the haphazard methods of the past. The precaution appears especially important inasmuch as most of the literature on this subject emphasizes infection as one of the major difficulties. Finally, the very badly infected, the hyperretentive types, may be all the better for a preliminary cystotomy. In effect, it consists of a transverse incision 5 cm. in extent, and about the same distance above the posterior aspect of the middle of the symphysis. Skin, subcutaneous fat and muscle sheath are thus incised; the muscle then bluntly separated in a longitudinal direction. The bladder, which has previously been partly filled, has an indwelling catheter with bulb syringe filled with metaphen solution. The underlying bladder is then palpated as it is further distended by this fluid. Sharp dissection then

exposes the organ which is also incised transversely. Advantages—there remains practically no space for drainage, the prevesical space is untouched and, as a consequence, absorption and infection are reduced to a minimum; hernia has never occurred and closure is effected on an average of twelve days; constitutional reaction is minimal; and finally, it has very materially reduced our operative mortality in open prostatectomy. The only reason that may be advanced for the customary longitudinal incision is precedent.

While it is true that endoscopic resection does not, as a rule, exert material effect on the nitrogen retention of the blood stream at all comparable to open prostatectomy, nevertheless, it is good practice to bring about a reduction of these elements to the patient's normal or pathological minimum. The foregoing methods are in conformity with the tenets of good medical practice, and any departure from these principles, fallacious.

Case Selection

Until endoscopic resection by whatever method achieves general acceptance as a replacement for prostatectomy, it is the part of wisdom to segregate these cases carefully and to allocate the procedure to the type of prostate, rather than arbitrarily force all types, regardless of conformation or pathological status, down the chute of any one method. No single method is all inclusive. It may very well be that time and inevitable technical advance will bring about this highly desirable situation, a claim made by some writers at the moment. In this evolutionary period, however, we are justified in making haste slowly. It is still my belief that the obviously infected, the very large prostates involving of necessity prolonged operations with excessive coagulation, the mechanically difficult, the intravesical types and especially the subtrigonal extensions, may be and as a rule are all the better for open operation.

For some years, I have employed for prostatic resection, an instrument conceived by me, designed and constructed by Frederick Wappler, called the Visualized Electrotome. It has come into universal use. Here, as in any revolutionary surgical procedure, the method has experienced its period of trial and error. It has been essayed by many individuals without the necessary preparatory training and surgical background. In this connection, every one of my publications on this subject has carried a warning of its technical difficulties. Despite this, the devotees of the

method are being constantly augmented. In a considerable number of qualified clinical centers, it has practically replaced open prostatectomy. It is now and always will be most exacting in its technical demands. I am still convinced, however, despite the extreme enthusiasm manifested by a number of recent contributors, that obstructing prostatism merits discriminating allocation of method to case, rather than case to method.

During these evolutionary years, it has been my constant endeavor to effect technical improvements, and to detect defects or deficiencies in technique. While this endoscopic vision is incomparably the best yet devised, and the illumination brilliant, the one weak point in its accomplishment is the operative removal at the floor of the vesical sphincter in the mid-line. Here, an unwary operator may inadvertently penetrate the trigon with the cautery loop. To obviate this defect we have adapted to the original Young punch, the panendoscopic telescope and a pistol grip.

At the moment, our present technique is to resect with this instrument the structures in proximity to the internal sphincter, using the cold punch; coagulate the bleeders with an electrode attachment, and complete the canalization as in a plastic operation, with the electric loop. If there be a single instrument or method sufficiently flexible to cope with the manifold aspects of obstructing prostatism, it is this so-called Visualized Electrotome. Nevertheless, our philosophy is that here we are dealing with a surgical entity, which can best be managed by a rational selection from diversified equipment.

Punch Method

It is our belief that the punch instrument, hot or cold, has a logical application only at or about the vesical neck; that the cold punch is cold only in the actual excision and must be supplemented by cautery or electric coagulation in the arrest of hemorrhage; and that for the precise removal of intraurethral intrusions of prostate anterior to the above mentioned point, the electrotome loop is much to be preferred. It should not be inferred that in our hands, the punch instrument is routinely employed, even in the restricted field for which it was constructed; rather be it understood that, with a diversified equipment, the instrument most appropriate for the condition is the one selected, just as in any other surgical procedure.

Complications

Before a navigator is assigned a post of considerable responsibility he must first experience fogs, storms, hurricanes and all the other vicissitudes incidental to the varying moods of the sea. So, too, must the qualified surgeon carry in his subconscious mind indelible impressions of trying and at times soul searching incidents in the course of his career, which enable him the better to meet similar emergencies which, from time to time, inevitably arise. Having experienced almost every complication associated with this particular field of surgery, I may therefore discuss with some authority the methods of their prevention.

Infection

This may be divided into the acute urosepsis and the late postoperative pyurias. With the acute type, our experience is limited to a very few cases. This we attribute to the fact that our cutting current has been of the tube type and relatively superficial in its action. Our interpretation of the etiology in our own cases was an infected background, incomplete preliminary sterilization, and excessive instrumentation immediately postoperative. The spark gap current is employed by us only for purpose of coagulation. One cannot help but wonder if the excessive use of the spark gap current, both for cutting and coagulation, may not be a contributing cause in the types of infection mentioned.

It is my understanding that in the act of cutting with the gap machine, only a portion of the current does the cutting, the rest of the current acting as a coagulant. As a consequence, there occurs a greater degree of tissue destruction. Obviously, therefore, a relatively bloodless operation is not necessarily a good one. Then, too, nature must laboriously throw off every last particle of coagulated tissue before complete convalescence has been achieved. With the tube type, there is a better cutting action and a more superficial sealing. This seems logical for the reason that the pieces excised with the gap machine are cooked if not carbonized, whereas the pieces removed by the tube type machine are susceptible of histological examination. On the other hand, it seems that the gap machine is better for subsequent coagulation and when not overdone may be quite superficial in its action.

The late pyurias have been more frequently observed. Turbidity of the urine may be a matter of a few weeks, but infections may persist. Generally speaking, they are asymptomatic and a matter of more con-

cern to the doctor than to the patient. Two cases come to mind. In one, the infection was completely controlled while urotropin was administered, only to return when it was withdrawn. This condition has since cleared up under the treatment later outlined. The organisms in this case were paracolon bacilli and enterococci. In the other, an asymptomatic pyuria continued about three years during which time the patient was perfectly satisfied, but I was neither contented nor satisfied. The organism in this case was non-hemolytic Staphylococcus albus. There was no response to treatment of any sort until two months ago when prontylin was administered together with an iron preparation. Quantitative hydrogen-ion readings with nitrazine paper were made. There promptly ensued a spectacular clearance of the urine and the same improvement in the microscopic slide of the prostatovesicular secretion. This condition has been maintained, the prontylin having since been withdrawn. This treatment is now routine in all our resection cases.

Observers at Bellevue Hospital have noted that in the employment of prontylin, it is unwise to administer other medicaments, even such simple preparations as milk of magnesia or aspirin. Repeated hemoglobin and red cell estimations should also be scrupulously carried out, because of possible anemia attending its administration. It may also be well to avoid coal tar products because of the possible presence of the sulphur radicle.

Indications

Preliminary knowledge of the bacteriology of urine and prostatic secretion is necessary. Anticipate infection by preoperative sterilization where possible. Try the method above described in suitable cases manifesting protracted pyurias. At operation, employ punctate coagulation of isolated bleeders and compression bag for venous ooze. Do not leave behind a cooked deep urethra. Avoid unnecessary instrumentation.

Bleeding incidental to operation or immediately postoperative is, we believe, best controlled by the method previously described. This has been our chief difficulty. Particular care should be observed in coagulation of isolated bleeders at the vesical aspect of the sphincter. It is at this point that the compression bag is least effective. A return flow free from macroscopic blood should be routine. The Foley compression bag and catheter constitutes one of the really important technical advances in this field. Foley calls attention to an interesting step in technique. In effect he advises that whenever the compression is not wholly satisfac-

tory the bag should be rotated. The obvious reason for this step is that the pressure may be uneven. The closed aseptic irrigating system devised by Drummond, a former resident, is another forward step in the achievement of technical perfection. A necessary requisite in the employment of this system of drainage is that the caliber of the system, catheter, connecting glass, and rubber tubing be uniform throughout. After all, it is simply a plumbing system, but even a plumber's apprentice would laugh to scorn the drainage apparatus one sees. Finally, it is important that the resident accompany the patient from the operating room to the bed and immediately establish drainage.

Every urologist knows that clot retention is the greatest factor in postoperative oozing. As a consequence, much thought has been given this matter. We have employed every known type of clot aspirator from the long established bulb evacuator to electric pump aspiration under vision. We are gradually coming to the conclusion that the simpler and less expensive the evacuator, the more general will be its employment. In a few cases of annoying ooze, following the advice of Kretschmer, we have used hot solutions of 1-5000 silver nitrate with gratifying results. A wise precaution in bladder irrigation in this type of case is the avoidance of undue distention of the organ. Two or three fluid ounces should be the maximum at any one time.

Hemoglobin estimation and red cell count before and after operation, as suggested by Gilbert Thomas, will supply interesting data in both closed and open prostatic operations. Persistent oozing should not be too long tolerated. Procrastination is not a good hemostatic. An endoscope or electrotome should be introduced and a search made for the bleeding points which are coagulated. Failing in this, and we have so failed on a number of occasions, subordinate pride and cystotomize, as previously described.

Urethral Stricture

The urethra of every patient should be calibrated before operation. It is a reasonable supposition that an occasional case may harbor a large caliber stricture (Ballenger's wise suggestion). Urethral stricture is undoubtedly an occasional complication; it is also an occasional complication of prostatectomy. It should be remembered that we are divulsing an encumbered urethra over a protracted period. Prior to the advent of this procedure, no urologist would think of leaving a No. 28 sound

domiciled in a patient's urethra for any such period of time. How to prevent the rare case of stricture is our concern. I have come to the conclusion that a water soluble lubricant is inadequate for the purpose. It is too soluble and too easily absorbed. The back and forth manipulation of the dry sheath may therefore cause a desquamation of the epithelial lining of the urethra, a precipitating factor in stricture formation. It should be remembered also that water soluble lubricants are extremely good conductors of electric currents. Moreover, I am authoritatively informed that the addition of the usual lubricating media to water greatly increases this conductivity. It seems to me that the entire urethra should be lubricated with some type of oil media, taking care that it does not escape into the bladder where it will befog the lens. The flash point of all lubricants should also be borne in mind. The flash point in all the oils used as lubricant, however, is very high. Further, if the instrument be removed for whatever cause, the anterior urethra should again be lubricated. I entertain the thought that with such precautions and with minimal operative time, stricture as a complication should prove a negligible factor.

Incontinence

At the moment of this writing, I cannot recall anything worse than an occasional case of temporary dribbling, which promptly cleared up. Of course, excessive coagulation or excision of tissue at the external sphincter may bring about such a condition. In an operation so precise as prostatic resection, this is an easily avoidable technical error.

Permanency

This is largely dependent upon the thoroughness of the resection. In my experience, all functional requirements are met when complete canalization has been established. One should be at pains to remove all lobulated intrusions, especially in the superolateral portion of the canal. This need not, however, be carried to the point of subtotal prostatectomy. This position is in conformity with the contention so frequently made, that when the obstruction is relieved, there is a recession of the residual prostatic tissue. Moreover, when instrumental prostatectomy is practiced, there is a concomitant increase in the time involved, as also in the amount of coagulation. Then, too, there is left behind a minimal amount of prostatic tissue which should serve as a protective barrier to adjacent

structures and, finally, the patient has lost his prostate.

Nor can I go along with those among my colleagues who so boldly attack sub-trigonal extensions of enlarged prostate with the electrically activated loop. The trigon is a triangular muscular platform which nature lays upon the bladder floor. When part of this structure is excised and infection ensues, a trigon thus infected may dissect itself away from the bladder wall proper, a very serious complication.

Mortality

Analysis of statistical tables of recent publications presents some incongruities. With some exceptions, the lowest mortality figures are presented by operators who are essentially instrumenteurs. Much higher figures, though still low, considered in terms of prostatic mortality, are submitted by urologists who have performed a great many resections, and who because of their broad training, are capable of coping with any contingency. Another interesting observation in a statistical survey by Orr, D. T. and Rue, L. R., is the citation of 14,104 resection cases as against 5,062 prostatectomies. Again, as might be expected, where 100 or less resections were performed, the mortality rate is considerably higher than with operators who have performed 500 or more operations —the penalty of apprenticeship. In general, it may be said that resection mortality, in competent hands, will probably vary between one and four per cent inclusive, depending on the risks assumed, and in individuals ranging from fifty to ninety or more years. It should also be stated that there is a progressive lowering of death rate in open surgery. It is quite within the realm of probability that the statistics from two-stage suprapubic prostatectomy, wherein the transverse approach to the bladder is employed, will approximate the above figures. Perineal prostatectomy, as a matter of fact, has always been notable for its low mortality. It is to be doubted if appendectomy performed in this age range could present a better report. It also compares quite favorably with figures from the Bureau of Vital Statistics.

Pertinent Factors

Low mortality seems to me overemphasized in the publications coming to my attention. Morbidity, a very important feature, is discreetly overlooked. Late symptomatic results, while for the most part satisfactory, are not as good as in prostatectomy. This communication is a

departure from the customary publications on endoscopic resection, wherein, as the writer has previously stated, there appears to be little if any mortality, operative incidents scarcely mentioned, and the patients inferentially living happily ever after. To make the story complete, this idyllic picture should be embellished with photographs of crutches discarded by these hitherto decrepit, but now obviously rejuvenated individuals.

With some notable exceptions, we seem, as previously stated, to have passed through the era of dogmatic assertion, contentious debate, inane sophistry and muddled conclusion. It must now be obvious that these revolutionary instrumental methods of correction of accomplished prostatic obstruction play a large and ever growing rôle. It has been the occasion of renewed research in open surgery of this gland, with resultant technical improvements, which prior to its advent had been somewhat static. Through its agency many individuals, who will not entertain the thought of open surgery, seem quite willing to submit to instrumental measures, thereby obviating the late sequelae.

It is an incontrovertible fact that after experiencing over a sufficient number of years a blazing cross fire of criticism (a wholesome thing), the enthusiasts, many of whom are in the front rank of urology, are more enthusiastic than ever; the middle-of-the-road group constantly growing in numbers, and the nihilists diminishing. Dr. Omar Elder, one of our beloved colleagues of the South, at a meeting of urologists held some years ago, in his fatherly way said, "Boys, you'd better get aboard this train, because if you don't, it's going to run right over you." To continue the aphorism, it would appear that too many of the boys are riding the cow-catcher. I elect the middle of the train and what seems to me, the right track.

With an enlightened public and an alert profession, the next generation of elderly men should escape the disabilities incidental to prostatic obstruction, as the prevention of this condition by these or similar methods, is altogether feasible.

Summary

An effort has been made here to set forth the vicissitudes encountered during the past years, with methods of avoidance, to the end that the profession at large may realize that the prostatic problem, despite the very real progress recently made, is still in a state of flux. This statement is as applicable to open surgery as it is to endoscopic methods.

THE SPECIFIC PREVENTION OF DIPHTHERIA

Further Observations and Inquiries

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The Problem in Canada

PRIOR to the introduction of agents for active immunization against diphtheria, no substantial reduction in the occurrence of that disease was evident in the Dominion of Canada.[1] Despite the fact that diphtheria antitoxin was made freely available to physicians by the public health authorities in almost all parts of the country, for prevention as well as treatment of diphtheria, the recorded morbidity rates maintained their previous high levels. That is not to say, however, that all efforts at control—isolation of cases and quarantine of contacts, separation of other members of the family, and prophylactic antitoxin—were entirely barren of results. The recorded morbidity rates of diphtheria are the resultants of different influences in different periods. For example, environmental changes, such as urbanization of the population, with greater opportunities for human contact, might well have given a real increase in cases in later years in the absence of any control measures; the wider use of laboratory services may have revealed cases otherwise undiagnosed; the use of public health nurses and school nurses may have resulted in more complete notification; and the changing clinical conception of the disease may have included as cases, types which would not have been included in earlier years. While correction cannot be made accurately for such factors, their possible influence on recorded rates cannot be neglected in making comparisons. Be that as it may, the case fatality rates and the specific mortality rates had been falling for over fifty years. But they were still high. From 1920 to 1924 the mortality ranged from 23.2 to 12.8 per 100,000 with 1200 to 2000 deaths or an average of 1600 as the annual toll. Over 40 per cent of that mortality was supplied by the 0-4 age group as shown in Table I. In that period, throughout Canada, diphtheria ranked as the chief cause of death in the

TABLE I

*Diphtheria deaths Canada registration area**

1921-25

Age	*Number*	*Per cent*
Under 1	271	5.8
1	306	6.6
2	397	8.6
3	486	10.5
4	472	10.2
0-4	1932	41.7
5-9	1723	37.2
10-14	611	13.1
15	369	8.0
Total	4635	100.0

* As Quebec Province did not join the Registration Area until 1926, this table does not include the data for that province.

age group 2-14, accounting for over 15 per cent or one in seven of all deaths in that age group.[2]

THE INTRODUCTION OF TOXOID

Not until 1925 was there general agreement among public health workers in Canada in respect of a suitable agent for immunization. In that year, as a result of the work of Ramon, diphtheria "anatoxine" or formol toxoid, prepared in the Connaught Laboratories, University of Toronto, was distributed to the provincial and local departments of health throughout Canada. This was done after careful laboratory and clinical studies had demonstrated its merit on the basis of innocuity and immunizing properties as a specific preventive against diphtheria.

The Reaction Test

Early experience showed that toxoid causes unfavorable reactions when given to certain individuals. The Reaction test, however, devised by our colleague, Dr. P. J. Moloney[3,4,5] made possible the detection of persons who might show untoward reaction if given toxoid. This has eliminated the fear of reactions and thus has greatly facilitated the wide use of toxoid. The Reaction test consists of the intradermal injection of 0.1 cc. of suitably diluted toxoid. A positive reaction, redness, indicates specific sensitivity induced by previous association with the diphtheria bacillus or by artificial immunization. A larger area of redness or, more particularly, of induration at the site is an indication of the likelihood of

that individual showing an untoward sensitivity reaction if given toxoid.[6] Such "reactors" are found mainly among older children and adults. The majority of reactors possess a high degree of antitoxic immunity and the incidence of diphtheria in them is much less than in their unselected controls.[7] It must be emphasized, however, that a positive reaction test in any individual is not proof of immunity. Antitoxin titrations reveal that some reactors have no detectable antitoxin ($< 1/500$ unit per cc. serum). Reactors may be readily immunized with diluted toxoid. In some instances the antigen in the test itself may be sufficient to complete the immunization. The number of positive reactions which may be found depends on several factors: age, diphtheria history and environment, and probably too on the material used. Wide variations in observations made in different places are therefore to be expected.

In Canada diluted toxoid has been used for the past twelve years, with advantage, as a control in the Schick test.[5]

The Limitations of the Schick Test

As the Schick test is used to a great extent in studies in diphtheria, especially in estimating the efficiency of various prophylactics, reference may be profitably made to certain of its limitations. The standards in various countries are not identical. For example, the International Standard and the standards laid down by regulation under the Therapeutic Substances Act of Great Britain and by regulation under the Food and Drugs Act of the Dominion of Canada differ from those prescribed by regulations of the Treasury Department of the United States of America (administered by the United States Public Health Service through the National Institute of Health).

In Table II is shown the disagreement found by using six different Schick tests in eighty-seven individuals.[8] It is evident that among both

TABLE II

Antitoxin titres correlated with the interpretation of Schick tests

Agreement of the 6 Schick readings	*Number*	*Antitoxin Titre*						
		<1/500	>1/250 <1/100	>1/100 <1/50	1/100	>1/50 <1/30	1/30	>1/20
All positive	33	33						
All negative	24		2	1	1	2		18
Non-interpretable	7	3					1	3
Frank disagreement	23	6			1	2		14
Total	87	42	2	1	2	4	1	35

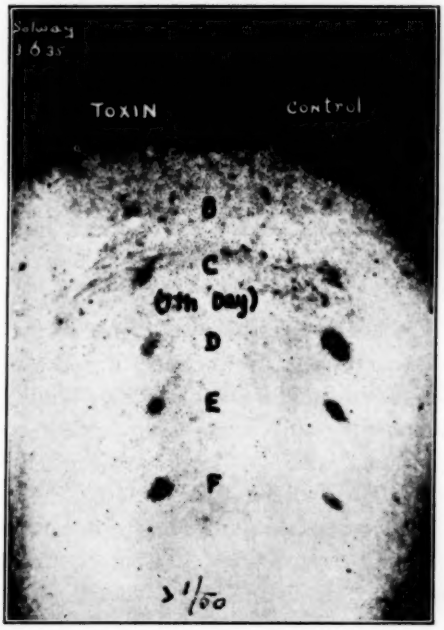

DIAGRAM I

those with high antitoxin content and those with no antitoxin (< 1/500) there was frank disagreement in the results. The table also shows that the lowest level of antitoxin associated with a Schick-negative state is about 1/250 unit. This is in agreement with the work of others.

In the accompanying illustration, Diagram I, are shown the results of six Schick tests done with six different products simultaneously in one individual who possessed more than 1/50 unit of diphtheria antitoxin per cc. of blood serum.[8] The lack of uniformity and the possibility of wrong interpretation need no further comment. Taylor and Moloney[9] have recently analysed fifteen Schick test preparations in regard to toxicity and combining power and correlated the results with the reactions obtained in individuals whose blood serum antitoxin was titrated. Their observations indicate clearly the desirability of revising Schick test requirements.

This must not be construed as undue criticism of the Schick test. It is an instrument which has yielded invaluable information in the epidemiology of diphtheria. Its inherent limitations including its fallacies

TABLE III

Diphtheria antitoxin response to antigens in children

Group	Antigen	Number Tested	Per cent distribution by antitoxin levels (units) 3 months after toxoid							
			1/500 and >	1/250 and >	1/100 and >	1/50 and >	1/20 and >	1/10 and >	1/5 and >	1/2 and >
1	3 doses, 15-20 Lf (2 cc.)	108	99	99	96	94	89	76	52	21
2	2 doses, 50 Lf (2 cc.)	105	80	70	60	45	35	*	15	5
3	2 doses, 20 Lf (2 cc.)	48	75	60	40	27	8	*	2	0
4	2 doses, 20 Lf (1.5 cc.)	48	60	50	29	17	15	*	15	4
5	1 dose alum ppt. (1 cc.)	40	97	*	67	40	*	15	*	12
6	2 doses alum ppt. (1 cc.)	36	97	97	97	86	86	39	25	*

* Not tested at this level.

must be understood, however, so that unwarranted conclusions be not drawn from the results obtained.

Comparison of Antitoxin Response to Various Antigens

In determining the antigenicity of various prophylactic preparations and in differentiating between them, the Schick test may be of little value.[10] While it will show a difference between a very poor prophylactic and a good one, it will not differentiate between two of a higher order of efficiency. For such differentiation, titrations of the blood antitoxin, as recommended by Fraser,[11,12] give much more reliable and complete information.

For full details in this connection reference should be made to the original publications. In Table III are shown the antitoxin responses induced by various prophylactic procedures.

It must be emphasized that these comparisons were made in children whose complete susceptibility was established prior to being given the prophylactic. In Group one the Schick test and Reaction test were used to select the children and all were frankly Schick-positive and Reaction test negative. In the other groups, antitoxin titrations of blood serum showed that all had initially less than 1/500 unit. This is, we think, most significant, as it is essentially for such individuals that prophylaxis is necessary. The suggestion that one or two doses of alum precipitated toxoid will give as satisfactory antitoxin response as that induced by three doses of unmodified toxoid is not borne out by these results.

Even more striking is the difference found in the duration of high antitoxin content, as shown in Table IV.

It is evident that at approximately one year after being given three

TABLE IV

Comparison of antitoxin titre after
A—1 dose alum precipitated toxoid B—3 doses unmodified toxoid
Original Titre <1/500

Per cent with	*After*					
	10 weeks		10-14 months		22-25 months	
	A	B	A	B	A	B
.01 or > units	68	91	22	97	15	86
.02 or > units	40	91	14	75	15	76
Number of children	40	35	36	32	26	21

doses of toxoid, over 90 per cent of thirty-two children still had 1/100 unit or more per cc. of blood serum in contrast to but 22 per cent retaining this level in a group of thirty-six children who had been given one dose of alum precipitated toxoid. At a two-year period the percentages showing 1/100 unit or more of antitoxin are eighty-six and fifteen for those given three doses of unmodified toxoid and one dose of alum precipitated toxoid respectively. The numbers of children in this comparison are not great, but the difference is far beyond chance variation.

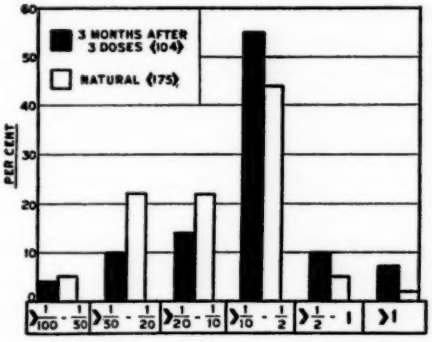

DIAGRAM II

Distribution by antitoxin levels of naturally and artificially immune persons

Gradual Decline in Antitoxin Content after Vaccination

It is gratifying to learn from Diagram II that the antitoxin content induced by three doses of toxoid is fully comparable and indeed slightly above that found in a sample of naturally immune persons. But it is as important, though less pleasant, to realize that as time passes after immunization, the level of antitoxin tends to fall. Fraser and Halpern have

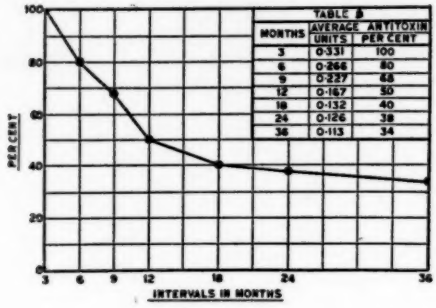

TABLE B

MONTHS	AVERAGE UNITS	ANTITOXIN PER CENT
3	0·331	100
6	0·266	80
9	0·227	68
12	0·167	50
18	0·132	40
24	0·126	38
36	0·113	34

TABLE V

Per cent antitoxin at intervals compared with the initial amount three months after three doses of toxoid

made antitoxin titrations in groups of children at various time intervals after three doses of toxoid. In this way one is able to obtain data not only on the levels of antitoxin of the individual but also on the average unitage of the group at specified intervals of time.

Table V shows the average (unitage) of each group at the intervals indicated and the percentage compared with the amount at the three-month period. These percentages are shown in the graph. At the one-year interval the average antitoxin content of the group as a whole is 50 per cent of the former level. It is of interest to note that the rate of loss is progressively less after twelve months. It will be realized that marked variations in the rate of loss of antitoxin will be found among individuals and that the rate may be changed significantly by the amount of diphtheria in the environment. In certain instances, if such chance contact with diphtheria bacilli be sufficient, the antitoxin may be increased, as shown by Fraser and Halpern. It must be pointed out that the results shown in Table V were obtained from the titrations of blood sera of children living in an environment practically free from diphtheria. Only in five instances was there evidence of increase in antitoxin content during the time of observation.

In a word, from the data quoted, it can be said that three doses of toxoid yield a higher level of antitoxin response and thus more durable antitoxic immunity than any other procedure compared to date; that the level induced by three doses of antitoxin is fully comparable with that found in natural immunes, but that this level tends to fall as the years pass following immunization.

TABLE VI

Reduction in Diphtheria in school children subsequent to toxoid, Toronto public schools, 1926-1930

Doses of Toxoid	*Cases*		Percentage Reduction	Deaths
	Estimated*	Actual		
One dose	34	24	29	3
Two doses	200	52	74	2
Three doses	222	23	90	0

* At rate in controls (schoolmates) under same exposure, corrected for age, etc.

The Protection against Diphtheria afforded by Toxoid

It is pertinent now to inquire into the actual value of toxoid in protecting children against diphtheria. For this purpose we have the amount of the diphtheria that occurred in children given one, two and three doses of toxoid, in comparison with the diphtheria in their school mates in Toronto public schools under the same exposure, as shown in Table VI.[7]

These observations were made when diphtheria was still very prevalent and represent therefore the results under conditions of high exposure. The group numbered over 27,000 children, while the controls were the balance of the school population, approximately 90,000. The inadequacy of one dose is at once apparent. The advantage of a second dose in immunization is evident in the greater reduction (74 per cent) of diphtheria in those given two doses of toxoid. The superiority of three doses is evident in the 90 per cent reduction of cases in the 16,829 children given three doses of toxoid in the 1927-1930 period. The difference in the results of two doses and three doses is beyond chance variation and is statistically significant. Further, and of importance, this difference is in general agreement with the difference in antitoxin responses induced by two or three doses of toxoid.

These observations were extended to include other school children given three doses of toxoid subsequent to 1930, making a total of 46,000, with the results shown in Table VII.[18] In each year the reduction in diphtheria in the group given three doses of toxoid approximated 90 per cent. In other words, this group suffered but 10 per cent of the rate of diphtheria suffered by their seat-mate controls. The study suggested, however, that as time passed after vaccination there was some falling off

TABLE VII

Reduction in diphtheria in children given three doses of toxoid, Toronto public schools, 1927-1932

Year	Cases		Percentage Reduction	Deaths
	Estimated*	Actual		
1927-1928	25	1	96	0
1928-1929	84	7	92	0
1929-1930	113	15	87	0
1930-1931	133	14	89	0
1931-1932	105	3	97	0
1927-1932	460	40	91	0†

* At rates in controls under the same exposure, corrected for age, etc.

† To the end of December 1937 there has been but one death from diphtheria in any child given three doses of toxoid in Toronto. This occurred in September 1935 in a child six and one-half years old who had been given three doses of toxoid five years previously.

in the degree of protection. This is entirely in keeping with the falling off in antitoxin content as shown by Fraser and Halpern and is additional evidence that immunity to diphtheria is a function of antitoxin. As is shown in Diagrams IV and V, subsequent to 1932 the paucity of diphtheria in Toronto yielded figures so small that deductions from them in regard to protection afforded by toxoid to vaccinated individuals were impractical.

The Control of Diphtheria Morbidity and Mortality

Gratifying as is the 90 per cent reduction in diphtheria in those given three doses of toxoid, as compared with their unvaccinated schoolmates, the actual benefit is not confined to those vaccinated, but is reflected in a reduction in diphtheria among their associates.

From 1925 to 1936 inclusive, sufficient toxoid has been distributed from the Connaught Laboratories for the immunization of over three million persons in Canada. It is not known precisely how much has been used, but the effect is evident in the strikingly lower rates of diphtheria morbidity and mortality in various cities and provinces in Canada. Diagrams III to VI are illustrative.

In Table VIII and Diagram III the history of diphtheria in the province of Ontario is briefly recorded. The population has increased from under two million in 1880 to over three and one-half million in 1936. In 1916 the Provincial Board of Health of Ontario provided for completely free distribution of diphtheria antitoxin. There were avail-

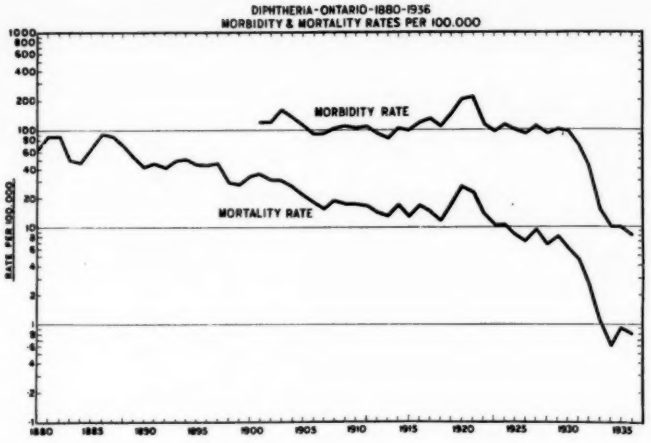

DIAGRAM III

able at the time, for physicians in Ontario, very satisfactory public health diagnostic laboratory facilities to aid in the diagnosis of diphtheria. Thus for more than three millions of persons the scientific weapons available twenty years ago, for the prevention and treatment of diphtheria, were readily accessible. Furthermore, physicians and the general public were repeatedly urged to take advantage of these facilities. Despite that fact, as has already been indicated, the free use of diphtheria antitoxin, while it may have influenced diphtheria mortality and case-fatality rates, showed little or no effect on the absolute volume of recorded diphtheria morbidity, and the essential lack of control of the disease is seen in the return to the high mortality rate of over 25 per 100,000 in 1920 and in the sustained high level of recorded morbidity, even after allowing for changing influences, for nearly thirty years. Then there is a precipitous decline such as had not occurred in the previous thirty years for which morbidity records are available, or in the previous fifty years for which mortality records are shown. From a rate of 97 in 1930, morbidity fell to 10 per 100,000 in 1934, and from a rate of 6 per 100,000 in 1930—the lowest on record till that date—mortality fell to 0.6 per 100,000 in 1934. This change has followed the extensive use of toxoid. The abruptness of the change in the picture coupled with the established efficiency of toxoid leaves no room for doubt that the change is due to active immunization. Any other hypo-

TABLE VIII

Diphtheria, Ontario, 1880-1936

Year	Deaths	Mortality Rate per 100,000	Year	Cases	Deaths	Mortality Rate per 100,000	Morbidity Rate per 100,000	Case Fatality Rate per 100 Cases
1880	1251	66.0	1901	2,627	772	35.4	120	29.4
1881	1704	88.4	1902	2,696	676	30.5	122	25.1
1882	1708	87.8	1903	3,599	687	30.5	160	19.1
1883	976	49.7	1904	3,045	608	26.6	133	20.0
1884	929	46.8	1905	2,641	503	21.7	114	19.1
1885	1282	64.0	1906	2,116	423	18.0	90	20.0
1886	1833	90.7	1907	2,172	380	15.9	91	17.5
1887	1786	87.6	1908	2,477	450	18.6	102	18.2
1888	1459	70.9	1909	2,635	430	17.5	107	16.3
1889	1101	53.0	1910	2,559	435	17.5	103	17.0
1890	893	42.6	1911	2,631	423	16.7	104	16.1
1891	952	45.0	1912	2,340	371	14.4	91	15.8
1892	890	41.9	1913	2,194	339	13.0	84	15.4
1893	1044	49.1	1914	2,772	443	16.7	105	16.0
1894	1075	50.3	1915	2,719	341	12.7	101	12.5
1895	942	44.0	1916	3,212	461	16.9	118	14.3
1896	925	43.1	1917	3,590	396	14.3	129	11.0
1897	976	45.3	1918	3,093	335	11.9	110	10.8
1898	634	29.3	1919	4,261	475	16.7	149	11.1
1899	599	27.6	1920	5,940	745	25.7	205	12.5
1900	738	33.9	1921	6,313	653	22.3	215	10.3
			1922	3,529	411	13.8	118	11.6
			1923	2,935	316	10.4	97	10.8
			1924	3,473	322	10.5	113	9.3
			1925	3,031	251	8.1	98	8.3
			1926	2,818	227	7.2	90	8.1
			1927	3,346	297	9.3	105	8.9
			1928	3,918	213	6.6	90	7.3
			1929	3,261	262	8.0	100	8.0
			1930	3,198	202	6.1	97	6.3
			1931	2,368	157	4.6	69	6.6
			1932	1,496	89	2.6	43	5.9
			1933	529	40	1.1	15	7.6
			1934	371	23	0.6	10	6.2
			1935	361	33	0.9	10	9.1
			1936	290	31	0.8	8	10.7

thesis to explain the change is superfluous. The fact that diphtheria has declined proportionately more than might have been anticipated from the number given toxoid is not difficult of explanation. Reducing cases in the immunized reduces foci of infection, spreaders of disease, in the group as a whole, so that the non-immunized benefit indirectly; this makes the control of diphtheria eminently practical. Further evidence of this is presented on page 578.

Hamilton, Ontario, a city of 150,000 population, was the first city of that size in Canada to control diphtheria effectively.[14] The achievement of Dr. James Roberts, Medical Officer of Health of Hamilton, has been a fine incentive to others. The record of this control is shown

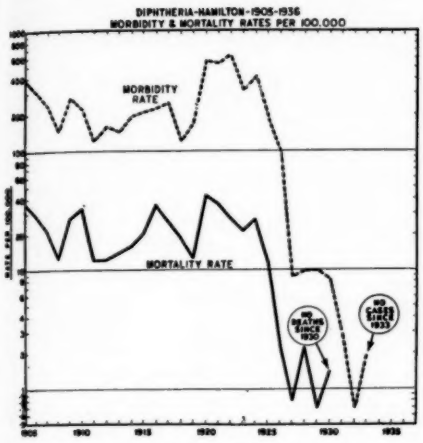

DIAGRAM IV

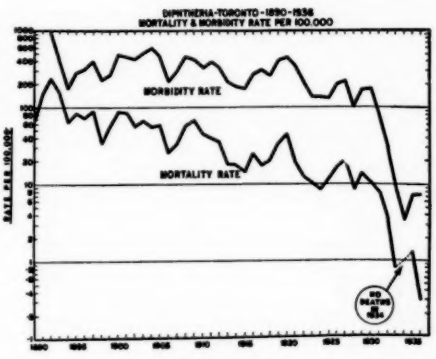

DIAGRAM V

in the above diagram (IV). There have been no deaths since 1930 and no cases since 1933. This record speaks for itself.

Diagram V shows the history of diphtheria in Toronto, Canada, a city of approximately 650,000 population. Since 1926, 104,000 children have been given three doses of toxoid by physicians of the Department of Public Health. It is estimated that 13,000 children have been given toxoid by their own physicians. The effect of this continued immunization is shown in the abrupt change in diphtheria, the morbidity rate falling from 164 per 100,000 in 1930 to 3.5 in 1934. In pre-toxoid years the annual toll was forty-five to ninety-eight deaths, an average of sixty-five from 1921 to 1925. For a period of fifteen months, from January 1934 to March 1935, not one death from diphtheria occurred in the city.*

The records of other smaller cities in Ontario, for example, Brantford, population (1936)—31,382, show even more satisfactory control of the disease.

Since 1922 free diphtheria immunization has been provided. No case of the disease has been reported since November 18th, 1930. Of the children born in 1937, 91 per cent have already received diphtheria toxoid.

Montreal, Quebec, a city of nearly 1,000,000 population, has experi-

* In the calendar year 1937, for the second time, no diphtheria death was reported in Toronto.

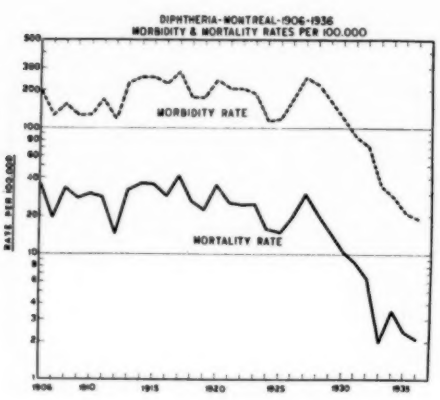

Diagram VI

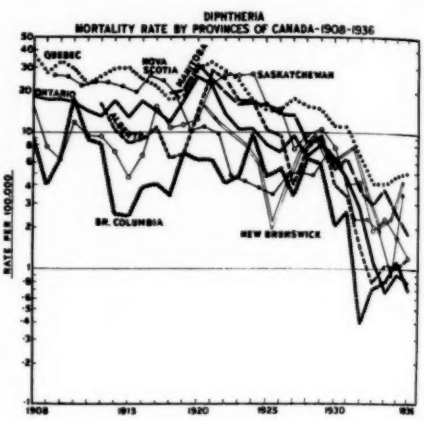

Diagram VII

enced a similar decline in diphtheria following the extensive use of toxoid, as shown in Diagram VI.

Diagram VII is given to show that every province of Canada has shared, though not equally, in the decline in diphtheria following the use of toxoid.

Reduction in the Incidence of Carriers

It has been suggested that specific immunization against diphtheria may occasion an increase in the carrier rate of virulent diphtheria bacilli in any community. Deadman[15] showed in 1932 that the experience in Hamilton, Ontario, was not at all in conformity with this suggestion. In 1920, 8261 cultures were examined for the diphtheria bacillus in his laboratory; 1040 were positive. In 1921, 9645 were examined and 1234 were positive. These data were typical of that time. In 1932, 3929 were examined and eighty-five (from twelve individuals) were positive. In 1934, out of 3817 examined, none were positive. Again in 1936, out of 3949 examined, none were positive.

From May 1934 to June 1936 surveys were made in Toronto in which approximately 7800 nose and throat cultures from the school children were examined.[12] Only four were found to contain virulent diphtheria bacilli. In another group of 999 children in an adjacent municipality, partly urban and partly rural, only two diphtheria carriers were

TABLE IX

Diphtheria, Toronto

Year	*Cases*	*Deaths*	*Number Examined*	*Positive Swabs*	*Summation of Persons Immunized**
1926	1098	90	13,231	2564	
1927	1223	114	12,286	1661	80
1928	593	50	9,354	827	12,492
1929	1030	82	16,542	2754	17,564
1930	1085	66	13,501	2109	18,954
1931	564	49	9,728	1086	35,280
1932	180	22	6,760	258	57,890
1933	58	5	5,077	86	72,367
1934	22	0	4,516	28	85,870
1935	46	8	4,322	56	92,918
1936	48	2	4,307	80	104,449

* Population: 1926—556,691
1936—645,462
Immunized—given three doses of toxoid.

discovered. In surveys of 1774 school children in Montreal in 1935-37, only two carriers were detected. Table IX shows the numbers of positive cultures found in routine work in the laboratories of the Department of Public Health in Toronto.

It is evident that in spite of a much greater number of cultures examined in relationship to the number of cases and a much more diligent search of the population, the number of carriers found showed very striking reductions. There is thus no evidence in these data in support of the suggestion that immunization of part of a community increases the hazard of diphtheria.

A comparison of the incidence of diphtheria in Canada, where vaccination against the disease has been widespread, with England and Wales, where a very limited amount of specific prophylaxis has been applied, is illustrated in Table X. It will be observed that for the weeks in 1937 and 1938 which are compared, the notified incidence of the disease in England and Wales is four to five times greater than has been recorded in the Dominion of Canada.

SUMMARY AND CONCLUSIONS

Prior to the use of toxoid there was no effectual control of diphtheria in Canada. In spite of the free distribution of antitoxin for prevention as well as treatment, recorded diphtheria morbidity persisted at its previous high levels, and mortality, though falling, still presented one of the most important public health problems.

TABLE X

Diphtheria cases reported Aug. 21, 1937 to Jan. 29, 1938

These rates are based on the estimated populations for 1936:
England and Wales—40,839,000
Canada —11,014,000

Week ending	*England & Wales*		*Canada*	
	Cases	Rate per 100,000	Cases	Rate per 100,000
Aug. 28	910	2.2	30	0.3
Sept. 4	1084	2.7	58	0.5
Sept. 11	1241	3.0	43	0.4
Sept. 18	1308	3.2	81	0.7
Sept. 25	1320	3.2	71	0.6
Oct. 2	1348	3.3	67	0.6
Oct. 9	1451	3.5	80	0.7
Oct. 16	1566	3.8	82	0.7
Oct. 23	1706	4.2	104	0.9
Oct. 30	1694	4.1	106	0.9
Nov. 6	1698	4.1	99	0.9
Nov. 13	1750	4.3	117	1.1
Nov. 20	1634	4.0	92	0.8
Nov. 27	1830	4.5	120	1.1
Dec. 4	1765	4.3	119	1.1
Dec. 11	1683	4.1	92	0.8
Dec. 18	1568	3.8	76	0.7
Dec. 25	1291	3.2	73	0.7
Jan. 1	1417	3.5	77	0.7
Jan. 8	1584	3.9	57	0.5
Jan. 15	1659	4.1	78	0.7
Jan. 22	1737	4.3	74	0.7
Jan. 29	1892	4.6	107	1.0

The Reaction test, as devised by Moloney, practically obviated the hazard of reactions and thus facilitated the wide use of toxoid.

Requirements for the Schick test are in need of revision and standardization. It is not infallible and its limitations should be recognized.

For determining the antigenicity of and differentiating between prophylactics the Schick test may be of little value. Antitoxin titrations give more complete and reliable information.

Titrations of the blood serum of children who initially had no antitoxin and were then submitted to various immunization procedures show that three doses of unmodified diphtheria toxoid induced a higher antitoxin response than any of the other procedures compared, namely, two doses of unmodified diphtheria toxoid, one dose of alum precipitated toxoid and two doses of alum precipitated toxoid. Titrations of blood serum of vaccinated children indicate a loss in antitoxin as time passes.

Field studies show that the reduction in diphtheria, in those vaccinated with two doses of toxoid, is, like the antitoxin response, less than the reduction in those vaccinated with three doses and that the diphtheria

occurring in the latter group is reduced by approximately 90 per cent as compared with that found in schoolmates under the same exposure.

Records show striking declines in diphtheria morbidity and mortality and in the incidence of carriers in various cities and provinces in Canada following the wide use of toxoid.

The abruptness of this decline in diphtheria morbidity and mortality and in the instance of diphtheria carriers in Canada following the extensive use of toxoid, the absence of any comparable diminution in the number of cases or of deaths from diphtheria prior to the use of toxoid, and the demonstrated efficiency of toxoid in preventing diphtheria in those vaccinated, leave no doubt that the decline is due to immunization.

The extent of the decline in several of the large cities and in certain of the provinces of Canada shows indubitably that diphtheria is a preventable disease.

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